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A1 *Sub 3*  
*B*  
73. (New) An interferon  $\beta$  polypeptide variant exhibiting an interferon  $\beta$  activity, comprising a variant sequence which differs from the wildtype human interferon  $\beta$  sequence SEQ ID NO:2 in no more than 15 amino acid residues and which comprises one or substitutions relative to SEQ ID NO:2 selected from the group consisting of:

- (a) Q49N+Q51S/T; and (b) F111N+R113S/T.

*2* 74. (New) The variant of claim *73*, wherein the variant sequence comprises the substitutions Q49N, Q51T, F111N, and R113T.

*3* 75. (New) The variant of claim *73*, wherein the variant sequence further comprises at least one substitution relative to SEQ ID NO:2 selected from: K19R; K33R; and K45R.

*4* 76. (New) The variant of claim *73*, wherein the variant sequence comprises the substitutions K19R, K33R, K45R, Q49N, Q51T, F111N, and R113T.

*5* 77. (New) The variant of claim *73*, wherein the variant sequence further comprises at least one substitution at a position relative to SEQ ID NO:2 selected from: M1; C17; N80; and V101.

*6* 78. (New) The variant of claim *73*, wherein the variant sequence comprises the substitutions C17S, Q49N, Q51T, F111N, and R113T.

*7* 79. (New) The variant of claim *73*, wherein the variant sequence differs from SEQ ID NO:2 in no more than 12 amino acid residues.

*8* 80. (New) The variant of claim *73*, wherein the variant sequence differs from SEQ ID NO:2 in no more than 10 amino acid residues.

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9 81. (New) A polypeptide conjugate exhibiting interferon  $\beta$  activity, which conjugate comprises

- (a) the variant of claim 73, and
- (b) at least one non-polypeptide moiety covalently attached to the variant.

10 9 82. (New) The conjugate of claim 81, wherein the non-polypeptide moiety is selected from: a polymer molecule, a sugar moiety, a lipophilic compound, and an organic derivatizing agent.

11 9 83. (New) The conjugate of claim 81, wherein the non-polypeptide moiety and the variant are directly covalently joined to one another, or are indirectly covalently joined to one another.

12 16 84. (New) The conjugate of claim 82, comprising at least one sugar moiety or at least one polymer molecule covalently attached to the variant.

13 17 85. (New) The conjugate of claim 84, comprising at least one sugar moiety and at least one polymer molecule covalently attached to the variant.

14 18 86. (New) The conjugate of claim 85, wherein the variant sequence comprises the substitutions Q49N, Q51T, F111N, and R113T.

15 19 87. (New) The conjugate of claim 86, wherein the variant sequence further comprises at least one substitution relative to SEQ ID NO:2 selected from: K19R; K33R; and K45R.

16 20 88. (New) The conjugate of claim 87, wherein the variant sequence comprises the substitutions K19R, K33R, K45R, Q49N, Q51T, F111N, and R113T.

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~~14~~ 89. (New) The conjugate of claim ~~81~~ <sup>9</sup>, wherein the variant sequence further comprises at least one substitution in a position relative to SEQ ID NO:2 selected from: M1; C17; N80; and V101.

~~15~~ 90. (New) The conjugate of claim ~~89~~ <sup>14</sup>, wherein the variant sequence comprises the substitutions C17S, Q49N, Q51T, F111N, and R113T.

~~20~~ 91. (New) The conjugate of claim ~~84~~ <sup>17</sup>, wherein the sugar moiety is covalently attached to an asparagine residue of the variant.

~~21~~ 92. (New) The conjugate of claim ~~91~~ <sup>20</sup>, wherein the sugar moiety is covalently attached to an asparagine residue of the variant selected from the group consisting Q49N, N80, and F111N.

~~22~~ 93. (New) The conjugate of claim ~~84~~ <sup>17</sup>, wherein the polymer molecule is covalently attached to a lysine residue of the variant.

~~23~~ 94. (New) The conjugate of claim ~~84~~ <sup>17</sup>, wherein the polymer molecule is covalently attached to the N-terminus of the variant.

~~24~~ 95. (New) The conjugate of claim ~~84~~ <sup>17</sup>, wherein the polymer molecule comprises a linear polyethylene glycol or a branched polyethylene glycol.

96. (New) An isolated nucleic acid comprising a nucleotide sequence encoding the variant of claim 73.

97. (New) A host cell comprising the nucleic acid of claim 96.

98. (New) An expression vector comprising the nucleic acid of claim 96.

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- A2 Control*
99. (New) A host cell comprising the expression vector of claim 98.
  100. (New) The host cell of claim 97 or 99, which host cell is a glycosylating host cell.
  101. (New) The host cell of claim 100, which glycosylating host cell is a CHO cell, a BHK cell, a HEK293 cell, or an SF9 cell.
  102. (New) A cell culture comprising the host cell of claim 97 or 99 and a culture medium.
  103. (New) The cell culture of claim 102, comprising the variant produced by expression of the nucleotide sequence.
  104. (New) The cell culture of claim 103, wherein the concentration of the variant is at least 800,000 IU/ml of medium.
  105. (New) A method of producing an interferon  $\beta$  polypeptide variant, the method comprising:  
providing a cell culture comprising the host cell of claim 97 or 99 and a culture medium;  
culturing the cell culture under conditions in which the variant is expressed; and  
recovering the variant.
  106. (New) The method of claim 105, wherein the host cell is a glycosylating host cell.
  107. (New) The method of claim 106, which glycosylating host cell is a CHO cell, a BHK cell, a HEK293 cell, or an SF9 cell.
  108. (New) A method for preparing a conjugate, the method comprising:  
providing the variant of claim 73;

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contacting the variant with a non-polypeptide moiety under conditions conducive for conjugation; and  
recovering the conjugate.

109. (New) A method for preparing a conjugate, the method comprising:  
providing a cell culture comprising the host cell of claim 97 or 99 and a culture medium;  
culturing the cell culture under conditions in which the variant is expressed;  
recovering the variant;  
contacting the variant with a non-polypeptide moiety under conditions conducive for conjugation; and  
recovering the conjugate.

110. (New) The method of claim 109, wherein the host cell is a glycosylating host cell.

111. (New) A composition comprising the variant of claim 73 or the conjugate of claim 81 and a pharmaceutically acceptable diluent, carrier, excipient or adjuvant.

112. (New) A method for treating a mammal with a disease for which interferon  $\beta$  is a useful treatment, comprising administering to the mammal an effective amount of the composition of claim 111.

113. (New) The method of claim 112, wherein the disease is multiple sclerosis.

114. (New) A method for treating a mammal having circulating antibodies against interferon  $\beta$  1a or 1b, which method comprises administering to the mammal an effective amount of the composition of claim 111.

115. The method of claim 112 or 114, wherein the mammal is a human.

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These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

#### REMARKS

##### Status of the Claims

Claims 1-72 are cancelled herein, without prejudice to subsequent renewal. Please note that Applicants reserve the right to file subsequent applications claiming the canceled subject matter, and that the claim cancellations should not be construed as abandonment of any presently or previously claimed subject matter or agreement with any objection or rejection of record.

Claims 73-115 are added herein. The claims are fully supported in the specification and add no new matter. Support for the term "variant" is found, for example, at least at page 13 lines 23-25. Support for substitutions recited in claim 73 are found throughout the specification, for example, at least at page 19 lines 17 to 21. Support for substitutions recited in claim 75 are found throughout the specification, for example, at least at page 32 lines 28-33. Support for substitutions recited in claim 77 are found throughout the specification, for example, at least at page 32 lines 28-33.

Claims 73-115 are pending with entry of this amendment.

##### Restriction

The invention is subject to a restriction requirement.

A. Claims 1-72 were restricted under 35 U.S.C. § 121, requiring Applicants to elect one of the following groups for prosecution in the present application:

Group I: Claims 1-53, drawn to polypeptide interferon conjugates (*Applicants note that the Examiner may have intended claims 1-51*), corresponding new claims 73-95;

Group II: Claims 52-56 and 66-72 drawn to DNA, vector, host cell and methods to produce protein, corresponding new claims 96-107 and 109-110;